Research Article

Sustainable Production of Reduced Phosphorus Compounds: Mechanochemical Hydride Phosphorylation Using Condensed Phosphates as a Route to Phosphite

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ABSTRACT: In pursuit of a more sustainable production of phosphorous acid (H_3PO_3), a versatile chemical with phosphorus in the +3 oxidation state, we herein report that condensed phosphates can be employed to phosphorylate hydride reagents under solvent-free mechanochemical conditions to furnish phosphite (HPO_3^{2-}). Using potassium hydride as the hydride source, sodium trimetaphosphate ($Na_3P_3O_9$), triphosphate ($Na_5P_3O_{10}$), pyrophosphate ($Na_4P_2O_7$), fluorophosphate (Na_2PO_3F), and polyphosphate ("$(NaPO_3)_n$") engendered phosphite in optimized yields of 44, 58, 44, 84, and 55% based on total P content, respectively. Formation of overreduced products including hypophosphite ($H_2PO_2^-$) was identified as a competing process, and mechanistic investigations revealed that

mechanochemical reduction of P(V) to P(III)

condensed phosphates → M^+H^- / via ball milling → phosphite

solvent-free · mild conditions · highly selective · sustainable

hydride attack on in-situ-generated phosphorylated phosphite species is a potent pathway for overreduction. The phosphite generated from our method was easily isolated in the form of barium phosphite, a useful intermediate for production of phosphorous acid. This method circumvents the need to pass through white phosphorus (P_4) as a high-energy intermediate and mitigates involvement of environmentally hazardous chemicals. A bioproduced polyphosphate was found to be a viable starting material for the production of phosphite. These results demonstrate the possibility of accessing reduced phosphorus compounds in a more sustainable manner and, more importantly, a means to close the modern phosphorus cycle.
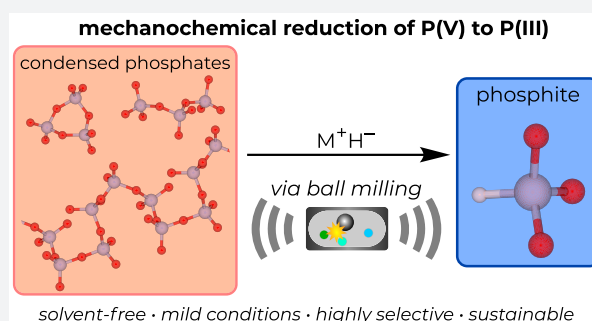
Phosphorous acid (H_3PO_3) and its conjugate base, phosphite (HPO_3^{2-}), have found applications as reducing agents, as cathode materials for lithium- and sodium-ion batteries,[1−3] as well as the starting material for other commercially important reduced phosphorus compounds, such as glyphosate.[4] Phosphite and related *H*-phosphonate esters are a family of key intermediates to organophosphorus compounds via elaboration of the P−H function into P−C bonds.[5−11] Recent advances in biotechnology have also cleared out a path for phosphite to act as an environmentally friendly herbicide, biostimulant, and biocide in modern agriculture owing to its minimal toxicity to humans and animals, biodegradability in soil, and inability to trigger eutrophication of natural water bodies through agricultural runoff.[12] The development of transgenic crops that metabolize phosphite rather than phosphate has allowed phosphite to serve as both a fertilizer and herbicide.[13,14] Additionally, phosphite is thought to have been a potential major nutrient in the preoxygenated Archaen oceans,[15] and the oxidation and condensation reactivity of inorganic phosphite likely mediated prebiotic formation of condensed phosphates.[16−19]

However, current production of phosphorous acid relies on a legacy process known as the thermal process, in which the phosphorus in phosphate rock is first reduced at 1500 °C to P(0) (white phosphorus, P_4), followed by oxidation back to P(III) as PCl_3 using chlorine gas. Subsequent hydrolysis provides phosphorous acid (Figure 1A).[20,21] This carbothermal legacy process is energy-intensive and involves substances that are environmentally hazardous.[22] Removal of phosphate from waste streams is imperative to ameliorate eutrophication and to meet ever more stringent environmental standards,[23] and the recovered phosphates constitute a valuable new input stream of this nonrenewable resource.[24−27] Among those phosphate recovery methods, one well-established process, known as enhanced biological phosphorus removal (EBPR), utilizes microorganisms to take up phosphate from wastewater and store it in intracellular polyphosphate granules.[28−30] In the "Heatphos Process", polyphosphate can be released from bacteria by heating at 70 °C for 1 h.[31,32] The recovered phosphate can be used as a raw material for the fertilizer industry.
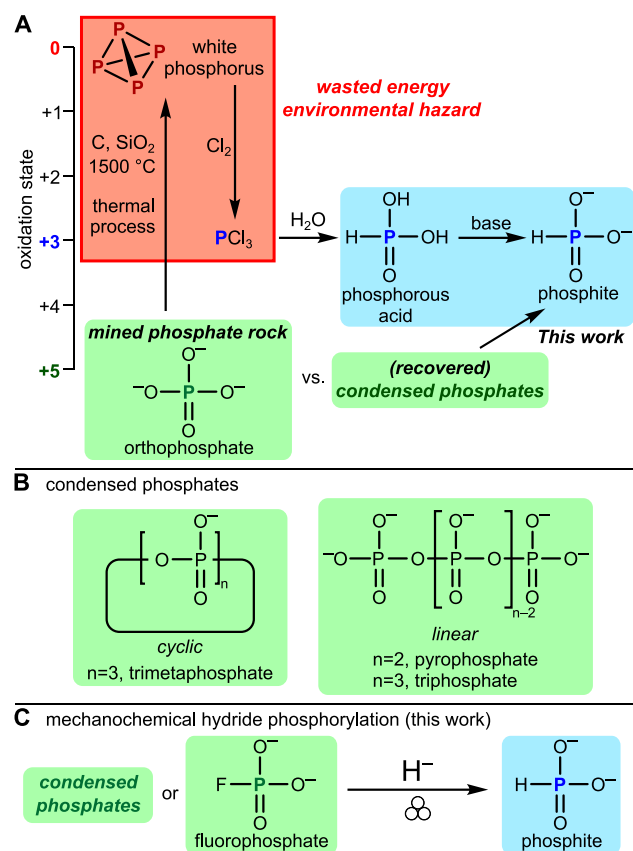
Figure 1. (A) Thermal process for the manufacture of phosphorous acid and phosphite (red) versus the envisioned new process to produce phosphite (cyan) from phosphate inputs (green) without traversing the lower oxidation states. (B) Structures of cyclic and linear condensed phosphates. (C) Reaction design of mechanochemical phosphorylation of hydrides using condensed phosphates or fluorophosphate (this work).

Recently, we showed that phosphate is a suitable precursor to chemicals traditionally synthesized from white phosphorus.[33−38] Building upon these principles, we sought to develop a process for the reduction of recovered phosphate to phosphite, bypassing hazardous white phosphorus and chlorine and minimizing energy waste (Figure 1A).[39] The envisioned reaction, hydride phosphorylation, can be considered as directly analogous to the canonical two-electron, one-proton reduction of a main-group element oxide: for instance, CO_2 reduction to formate.[40,41]

Our curiosity in regard to this topic was piqued by the industrial synthesis of sodium fluorophosphate (Na_2PO_3F), an active ingredient in toothpaste. In a 100% atom-efficient reaction, sodium trimetaphosphate ($Na_3P_3O_9$) and 3 equiv of sodium fluoride are heated to 300 °C resulting in a melt and the formation of Na_2PO_3F (eq 1):[42]

$$Na_3P_3O_9 + 3NaF \xrightarrow{300°C} 3Na_2PO_3F \tag{1}$$
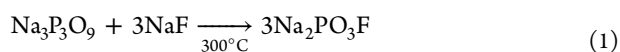
Sodium trimetaphosphate ($Na_3P_3O_9$), readily produced by the dehydration of phosphoric acid with sodium chloride,[43] is the smallest cyclic phosphate with an O:P ratio of 3 (Figure 1B), identical to that in phosphite. It is therefore an attractive starting material for reduction to produce phosphite. In analogy to the industrial production of Na_2PO_3F, we hypothesized that the reaction of $Na_3P_3O_9$ with a metal

hydride such as sodium hydride (NaH) might give rise to the formation of sodium phosphite (Na_2HPO_3) (eq 2):

$$Na_3P_3O_9 + 3NaH \rightarrow 3Na_2HPO_3 \tag{2}$$

Along the lines of the synthesis of Na_2PO_3F, our initial strategy involved the thermal reaction between NaH and $Na_3P_3O_9$ (neat, 3:1 molar ratio) at 300 °C, and we were pleased to observe the formation of the desired phosphite by ^{31}P NMR spectroscopy. However, the presence of unreacted trimetaphosphate as the major phosphorus-containing species at the end of the reaction sequence pointed toward poor conversion. Additionally, the formation of an unusual phosphinophosphate, $[H_2P-OPO_3]^{2-}$, which is tentatively assigned based on data from NMR spectroscopy, suggested poor mixing of the solid reagents and high local concentrations of hydride, plausibly leading to overreduction.

In order to overcome this issue, we turned to mechanochemistry. Protocols in which reagents are subjected to intimate mixing and grinding using ball mills have become increasingly popular in recent years, affording reaction products that cannot be obtained using traditional solution-based methods.[44−50] Additionally, the use of mechanochemistry obviates the need for solvent and can give short reaction times, good scalability, and even opportunities for in situ reaction monitoring.[51,52] Mechanochemical P-centered nucleophilic substitution has been applied to build P−O(N) bonds in small molecules[53−61] and functional polymers.[62,63]

Ball-milling reactions were conducted in a shaker mill using steel jars and ball bearings, using commercial hydride sources and thoroughly dehydrated phosphates. All water-soluble phosphorus-containing products were quantified by ^{31}P NMR analysis of an aqueous extract of the solid reaction mixture, and percentage yields and recovery rates of extraction are based on total P content in the phosphate input. The reaction of $Na_3P_3O_9$ with 3 equiv of NaH (H:P = 1:1) led to the formation of the desired product in short reaction times (within 60 min) with almost complete consumption of the starting material (Table 1). Other major products included pyrophosphate and orthophosphate. Control experiments confirmed that these phosphate materials did not appear simply by ball-milling $Na_3P_3O_9$ alone under otherwise identical conditions, although $Na_3P_3O_9$ was partially converted to a variety of cyclic and linear phosphates (SI section 5.2.2).

Having observed formation of the desired product, we set out to optimize the hydride reagent. An initial survey of hydride sources at stoichiometric loading (H:P = 1:1) showed that potassium hydride (KH) gave superior results to other common hydride reagents in regard to conversion of phosphate input and yield of phosphite (Tables 1 and S1). The lower lattice energy of KH likely contributes to its higher reactivity at the crystal surface.[64] On account of the higher yields obtained using KH, we chose to use it as the hydride source to continue our study. Use of KH as the reductant also avoided the accumulation of phosphorylated phosphite (isohypophosphate, $[O_2HP-OPO_3]^{3-}$),[16,65−67] which was formed using other hydride reagents.

During the course of optimization, we also identified hypophosphite ($H_2PO_2^-$), a species containing phosphorus in the +1 oxidation state, as a product of ball-milling. In addition, a phosphorus recovery rate of only 81% suggested formation of insoluble or gaseous side products (presumably elemental phosphorus and phosphine gas, respectively). These findings pointed toward a non-negligible portion of $Na_3P_3O_9$ under-

Table 1. Optimization of the Hydride Source[a]
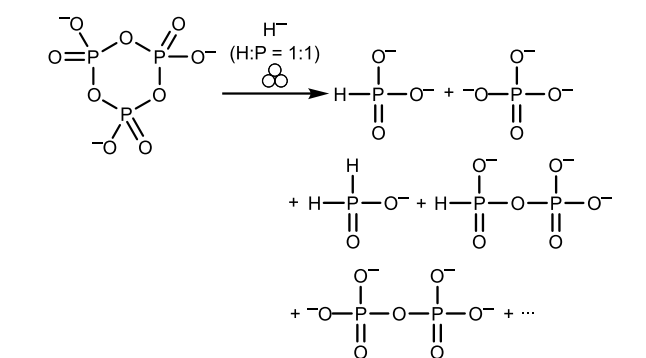
hydride	phosphite yield[b,c,d] (%)	conversion[b] (%)
LiH	17	99
NaH	10(16)	95
KH	23	>99
NaBH$_4$	11(18)	92
LiAlH$_4$	6(9)	82

[a]Reaction conditions: Na$_3$P$_3$O$_9$ (1.0 mmol), alkali metal hydrides (3.0 mmol) or NaBH$_4$ (0.75 mmol) or LiAlH$_4$ (0.75 mmol), 30 Hz, 60 min. [b]Determined by ^{31}P NMR spectroscopy. [c]Based on total P content. [d]Parenthesized value includes phosphite in free and phosphorylated forms when phosphorylated phosphites were observed.

going overreduction to yield species in the lower oxidation states. Overreduction consumes hydride equivalents, thereby reducing the yield of phosphite, and also poses a danger to the environment as phosphine gas is known to be highly toxic.[21]

In pursuit of a better yield and selectivity of reduction to phosphite, we explored the scope of phosphate sources (Tables 2 and S2). We first tried linear phosphates (pyrophosphate and

Table 2. Scope of Phosphate Sources and Effects of Hydride Loading[a]

		yield[c] (%)		
phosphate	H:P[b]	HPO$_3^{2-}$	H$_2$PO$_2^-$	recovery[d] (%)
Na$_3$P$_3$O$_9$	1:1	23	2	81
K$_4$P$_2$O$_7$	1:2	30[60][f]	0	98
Na$_4$P$_2$O$_7$	1:2	37[74][f]	0	98
Na$_4$P$_2$O$_7$[e]	1.5:2	44[88][f]	0	97
K$_5$P$_3$O$_{10}$	2:3	31[47][f]	0	98
Na$_5$P$_3$O$_{10}$	2:3	44[66][f]	trace	96
Na$_5$P$_3$O$_{10}$[e]	1:1	58[87][f]	0	98
Na$_2$PO$_3$F	1:1	47	2	93
Na$_2$PO$_3$F[e]	1.5:1	84	0	99
Graham's salt	1.0:1	29	2	85
Graham's salt[e]	1.5:1	55	4	94
K$_3$PO$_4$	1:1	0	0	97

[a]Reaction conditions: 1.0−3.0 mmol of P, 30 Hz, 60 min. [b]Ratio of hydride to total P content. [c]Based on total P content and determined by ^{31}P NMR spectroscopy. [d]Defined as recovery efficiency of total P content by aqueous extraction, determined by ^{31}P NMR spectroscopy. [e]90 min. [f]For well-defined polyphosphates P$_n$O$_{3n+1}^{(n+2)-}$, the bracketed value of yield is based on $(n-1)$ reactive P-units according to eq 3 (two for triphosphate, one for pyrophosphate).

triphosphate) that are industrially accessible by dehydration of hydrogen or dihydrogen phosphate at 300−900 °C.[21] Unlike cyclic phosphates, each polyphosphate molecule P$_n$O$_{3n+1}^{(n+2)-}$ contains only $(n-1)$ P-units that are susceptible to hydride attack, namely, in theory, a polyphosphate with n P-units can only produce $(n-1)$ equiv of phosphite with 1 equiv of orthophosphate as a byproduct (eq 3):

$$P_nO_{3n+1}^{(n+2)-} + (n-1)\,H^- \xrightarrow{\;\;\;} (n-1)\,HPO_3^{2-} + PO_4^{3-} \quad \text{(3)}$$
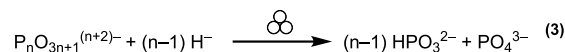
The reaction of sodium pyrophosphate (Na$_4$P$_2$O$_7$) with 1 equiv of KH (H:P = 1:2) furnished phosphite in a 37% yield within 60 min of mixing. While elongating the reaction time at the same hydride loading did not improve the yield, an increased yield of phosphite (44%), which corresponds to 88% of reactive P-units, was obtained when a higher hydride loading (H:P = 1.5:2) was used followed by 90 min of mixing. A similar trend was observed in the reduction of sodium triphosphate (Na$_5$P$_3$O$_{10}$) by KH. Mixing Na$_5$P$_3$O$_{10}$ with 2 equiv of KH (H:P = 2:3) yielded phosphite in 44% yield within 60 min, while an increased yield of phosphite (58%), which corresponds to 87% of reactive P-units, was obtained at a higher hydride loading (H:P = 1:1) after 90 min. Only a very low degree of overreduction was observed. Potassium phosphate salts react with KH in a similar fashion to sodium salts but more slowly.

Sodium fluorophosphate (Na$_2$PO$_3$F) engendered a moderate yield (47%) and a notable degree of overreduction within 60 min using 1 equiv of KH (H:P = 1:1). The use of an excess of KH (H:P = 1.5:1) resulted in a remarkably improved yield (84%) and diminished overreduction within 90 min of mixing. Commercial "sodium hexametaphosphate" or Graham's salt, which is a mixture of mainly linear polyphosphates of various chain lengths (92% P) and minor cyclic phosphates (Figure S10), afforded a low yield of 29% using stoichiometric KH (H:P = 1.0:1). Using a higher loading of KH (H:P = 1.5:1) instead, an increased yield of 55% and a notable buildup of hypophosphite (4%) were afforded. Lastly, orthophosphate gave rise to no phosphite, confirming that the presence of phosphoanhydride bonds is key to such reduction reactivity by loss of phosphate as a leaving group. The reactivity of phosphoanhydride bonds predominates biological phosphorylation processes, which involve removal of a terminal PO$_3^-$ group, such as in processes that consume ATP and produce ADP.[68]

Mechanochemical reduction of Na$_4$P$_2$O$_7$ by KH followed by treatment with deuterium oxide (D$_2$O) resulted in no detected deuterium incorporation in the formed phosphite as determined by ^{31}P NMR spectroscopy, indicating that KH was the only source of hydrogen atoms. This result confirmed phosphorylation of hydride as the exclusive mechanism of phosphite P−H bond formation in the current system, ruling out a mechanism of KH reduction of phosphates to yield H-free low-oxidation-state phosphorus intermediates followed by protonation during aqueous workup.

To further improve the yield and alleviate generation of hazardous side products, we set out to seek the chemical origin of overreduction. First, we investigated the stability of phosphite toward hydride. No conversion was observed when sodium phosphite (Na$_2$HPO$_3$) was ball-milled alone or treated with KH under typical reaction conditions, ruling out disproportionation[69,70] or hydride attack on phosphite as an
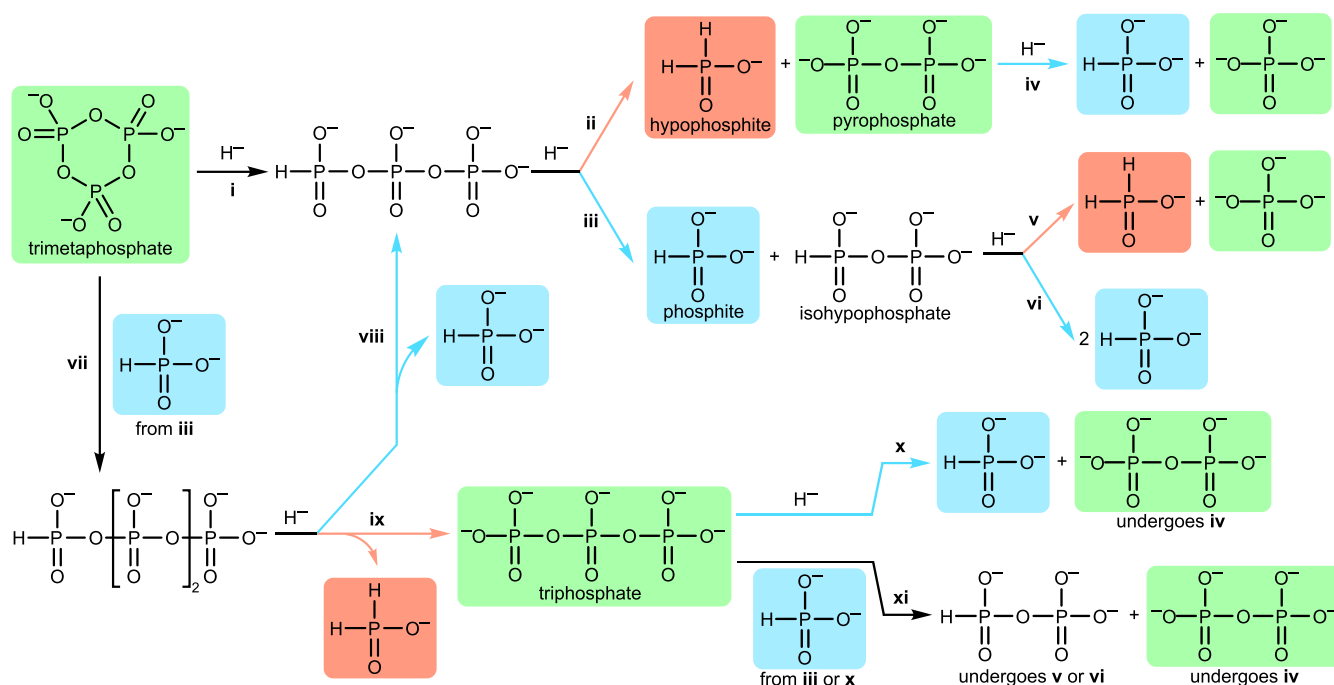
Figure 2. Proposed pathways for phosphite (cyan) and hypophosphite (tangerine) formation from select condensed phosphates (green) applied as phosphate inputs and/or involved as intermediates.

overreduction pathway. We then studied the reactions of polyphosphates with various equivalents of hydride (Table S3). Treatment of pyrophosphate with 0.5 equiv of KH (H:P = 0.5:2) furnished phosphite with good efficiency (74% based on hydride) without detected overreduction. However, reactions of sodium triphosphate ($Na_5P_3O_{10}$) with substoichiometric KH (H:P = 1:3) resulted in a decreased yield of phosphite (60% based on hydride after 60 min, Table S3, entries 7 and 8) and observation of hypophosphite ($H_2PO_2^-$), an overreduction product not detected when higher hydride loadings were applied (Table S3). Also identified in the reaction were isohypophosphate ($[O_2HP-OPO_3]^{3-}$) and other phosphorylated phosphites (SI section 5.4), from which hypophosphite is generated via nucleophilic substitution with hydride (Figure 2ii,v,ix). These results suggested that, counterintuitively, reducing the amount of hydride employed has led to an increasing tendency for overreduction. A plausible rationale for this is that phosphite, the desired product, can undergo phosphorylation under the reaction conditions (Figure 2xi) thereby activating it for a second reduction by hydride (Figure 2v). While direct hydride attack at the bridging P-group in triphosphate as a pathway toward phosphorylated phosphite cannot be ruled out at this point, such a rise in overreduction is primarily attributed to phosphorylation of generated phosphite. Characterization of the reaction of Na_2HPO_3 with $Na_5P_3O_{10}$ by ^{31}P NMR spectroscopy revealed that phosphite is susceptible to phosphorylation by triphosphate under typical reaction conditions to afford isohypophosphate, which may give rise to overreduction (SI section 5.3.2). Because this process is in competition with phosphate reduction (Figure 2vi,x), adding excess KH mitigates phosphorylation of phosphite by depleting reactive polyphosphates in the system and thus leading to diminished overreduction. In contrast, pyrophosphate was found to be inefficient at phosphite phosphorylation under these conditions (SI section 5.3.1), explaining the lack of overreduction in its reactions. The

observed behavior can be attributed to the diminished leaving group capacity of orthophosphate relative to linear condensed phosphates. Sodium fluorophosphate (Na_2PO_3F) was also found to be a potent phosphorylating reagent toward phosphite under mechanochemical conditions (SI section 5.3.4). The diminished overreduction of Na_2PO_3F using an excess of KH suggests the mitigation of phosphorylation of phosphite, as in the case of $Na_5P_3O_{10}$.

The reactions of sodium trimetaphosphate ($Na_3P_3O_9$) with KH displayed a higher degree of overreduction (with up to 7% yield of hypophosphite; Table S3, entries 1−6) compared to the reactions of pyrophosphate and triphosphate. When $Na_3P_3O_9$ was treated with substoichiometric KH (H:P = 1:3), phosphorylated phosphites of various chain lengths were the major reduction products instead of free phosphite (SI section 5.5), pointing toward a mechanism of hydride phosphorylation through ring opening followed by stepwise cleavage of terminal phosphates (Figure 2i,iii). The ring opening reactivity of trimetaphosphate, which has been observed in the reaction with ammonia in aqueous media,[71−73] was further demonstrated by the facile mechanochemical reaction between $Na_3P_3O_9$ and Na_2HPO_3, affording phosphorylated terminal phosphites of various chain lengths (Figure 2vii), which were assigned based on a combination of 1D- and 2D-^{31}P NMR spectroscopic techniques (SI section 5.3.3). These results suggest that the ring-opening reactivity of trimetaphosphate provides additional pathways to form phosphorylated phosphites and thus significantly increases the degree of overreduction.

Although the major component of commercial Graham's salt is long-chain linear polyphosphates, the reactions of Graham's salt with KH engendered up to 4% yield of hypophosphite. Efforts to understand the reactivity of long-chain linear polyphosphate in depth are complicated by not only the presence of cyclic phosphate impurities in commercial polyphosphates but also the propensity to yield a polydisperse

mixture of linear phosphates under mechanochemical conditions even if a monodisperse polyphosphate is employed as starting material (as demonstrated using $Na_5P_3O_{10}$; SI section 5.2.1). Nonetheless, Graham's salt (using the general formula $NaPO_3$) was found to undergo facile mechanochemical reaction with Na_2HPO_3, yielding phosphorylated phosphites more efficiently than $Na_5P_3O_{10}$ does (SI section 5.3.5). Therefore, it is plausible to hypothesize that long-chain linear polyphosphates are prone to a higher degree of overreduction than triphosphate is.

Despite having only one reactive P-unit per molecule, sodium pyrophosphate is a useful phosphate source due to its highly selective and efficient conversion to phosphite. Therefore, we carried out phosphite isolation studies using $Na_4P_2O_7$ as a starting material. Isolation of phosphite from phosphates in the crude mixture was achieved through precipitating orthophosphate as struvite ($NH_4MgPO_4 \cdot 6H_2O$), taking advantage of the low solubility of this mineral.[74] This method led to a 34% isolated yield of phosphite (67% based on reactive P) in the form of a barium phosphite salt $BaHPO_3 \cdot H_2O$ (SI section 4.5). Phosphorous acid solutions can be prepared by treatment of the barium phosphite salt with sulfuric acid,[75] and protocols for separation of phosphorous acid from phosphoric acid on an industrial scale are well-established.[76−79]

In biological systems, long-chain polyphosphate (polyP) is involved in ATP synthesis catalyzed by polyP kinases, in which polyP is the source of a third $PO_3^−$ group leading to ATP.[80,81] Inspired by the biochemical reactivity of polyP, we turned our attention to the application of bioproduced polyP as a source of $PO_3^−$. A recent protocol of polyP accumulation using *Saccharomyces cerevisiae* (baker's yeast) followed by isolation allowed us to obtain bioproduced polyP (bio-polyP, Figure 3) in multigram quantities.[82,83] The composition and structure of

the isolated bio-polyP was analyzed by ^{31}P NMR spectroscopy in conjunction with several elemental analytical methods. Linear phosphates (with Na^+, Mg^{2+}, K^+, and Ca^{2+} as counterions) constitute 77.8 wt % of bio-polyP with an average degree of polymerization of 37, whereas residual orthophosphate and trimetaphosphate are <1.5 wt %. The measured metal composition and average chain length of the isolated bio-polyP are similar to those of intracellular polyphosphates in bacteria in EBPR systems.[84,85] Major impurities include residual organic substances (protein and nucleic acid), water, and NaCl.

Mechanochemical reduction of bio-polyP with excess KH (H:P = 2.0:1) on a 0.2 g scale afforded phosphite in 28% yield. Instead, a high yield of orthophosphate (67%) was observed and is partially attributed to the interference from oxygen-containing impurities including water and residual organic mass.

Preliminary experiments revealed that the affecting impurities can be partially removed through vacuum calcination. While bio-polyP is labile upon heating under air at 120 °C as well as under ball-milling conditions, affording orthophosphate and short-chain polyphosphates (SI section 7.1), calcination of bio-polyP at 500 °C under reduced pressure pyrolyzes organic impurities and removes the water content. The resulting dark material (Figure 3 inset) cannot be effectively extracted with water, but a ^{31}P NMR spectrum of its aqueous extract still confirmed long-chain polyphosphate as the predominant form of P. Calcined bio-polyP engendered an increased phosphite yield of 42%.

In conclusion, we have demonstrated that phosphite can be accessed via direct reduction of condensed phosphates (or fluorophosphate) by simple metal hydrides, using mechanochemical methods. Unlike the thermal process, this direct process bypasses the hazardous intermediate white phosphorus and ostensibly does not traverse lower phosphorus oxidation states than +3. This process avoids the use of carbon as a stoichiometric reductant in contrast to the thermal process that is inherently carbon-intensive and can be decarbonized by using renewable energy to power the production of raw materials (potassium, sodium, and hydrogen gas) used to generate KH.[86,87] Optimization of reaction conditions revealed that high phosphite production yields and good selectivity can be achieved when employing triphosphate, pyrophosphate, and fluorophosphate as phosphate sources with KH as the hydride source. The optimized protocol employing pyrophosphate, which contains only the poor leaving group orthophosphate, gives high selectivity for the targeted P(V)→ P(III) reduction. Mechanistic studies revealed that (poly)phosphorylated phosphite species that are generated through either ring opening of cyclic phosphates by hydride or phosphorylation of formed phosphite are key intermediates in the overreduction pathways observed when not using pyrophosphate as the P source. By using bioproduced polyphosphate from baker's yeast, we demonstrated that polyphosphates recovered from microorganisms could be promising starting materials for sustainable production of phosphite, while certain impurities may be detrimental to the efficiency of production. With this case study, we lay down an idealized framework for generating an industrially useful P(III) chemical that bypasses toxic and high-energy intermediates and presents an opportunity to move toward a "closed-loop" phosphorus industry.
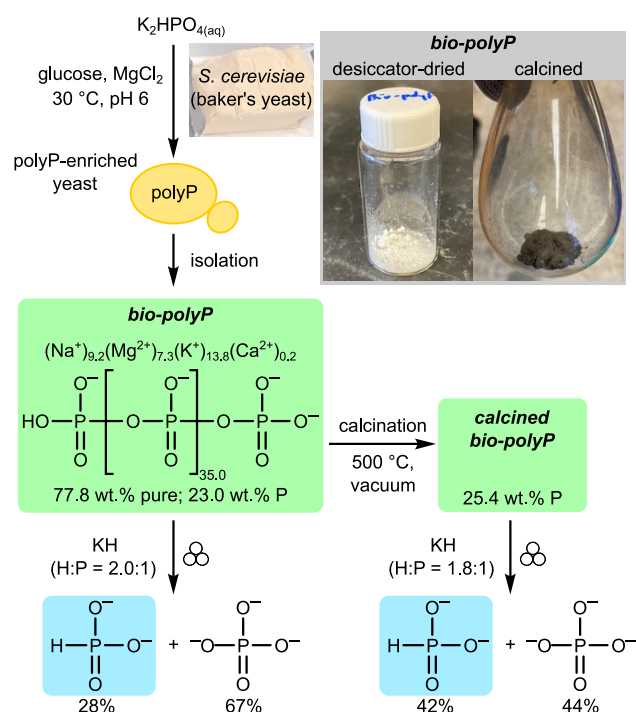
Figure 3. Biotechnological production, properties, and mechanochemical reactivity of bio-polyP. Inset: Photos of a bio-polyP sample dried in a desiccator at 25 °C (left) and a bio-polyP sample after calcination (right).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscentsci.1c01381.

> Experimental details of mechanochemical reactions, characterization data, and protocol for accumulation and isolation of bio-polyP from baker's yeast (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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